Effect of opioids and benzodiazepines on clinical outcomes in patients receiving palliative care; an exploratory analysis

Short title: Impact of drug class on clinical outcomes

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Abstract

Background: Medications for symptom management in palliative care have associated, but poorly understood, harms. Drug-related harms have important clinical implications, may impact on patients' compliance and contribute to symptoms.

Objective: To explore the longitudinal relationship between oral morphine equivalent daily dose (MEDD) and oral diazepam equivalent daily dose (DEDD) with functional, cognitive and symptom outcomes. in patients receiving palliative care.

Design: Secondary longitudinal analysis of cancer decedents (n=235) from a palliative care randomised controlled trial with multiple outcome measures. At each time-point, MEDD and DEDD were calculated. Multilevel modelling was used to investigate independent associations between MEDD and DEDD, and cognitive and gastrointestinal symptoms, quality of life, performance status and survival.

Setting/Subjects: Participants were recruited from a specialist palliative care programme in Southern Adelaide, were expected to live ≥48 hours, had pain in the previous three months and a baseline Folstein Mini-Mental Status Examination score ≥25.

Results: Cognitive and gastrointestinal symptoms, performance status, and quality of life worsened over time. In the adjusted multilevel analysis, statistically significant relationships remained between MEDD/DEDD and worsening performance status ($p=0.001$), DEDD and gastrointestinal effects ($p<0.001$), MEDD and quality of life ($p<0.022$).

Conclusions: Commonly used palliative medications were associated with deteriorating performance status. The lack of association between MEDD with gastrointestinal or cognitive symptoms underlines that these associations are not inevitable with close attention. This analysis highlights the importance of including other medications as confounders when exploring

medication-related harms. An understanding of the risk-benefit balance of medications is needed to maximise net benefits for patients.

Key words

Opioids, benzodiazepines, palliative, cancer, symptoms, disease trajectory, survival, quality of life, adverse medication events

Background

Patients accessing palliative care services receive many medications, each with benefits and harms.[1-4] Drug-related harms may influence patients' compliance.[2,5-8] Opioids and benzodiazepines are frequently prescribed and co-prescribed for symptom management but have toxicities such as gastrointestinal dysfunction and cognitive impairment.[9-15] Long-term opioids and benzodiazepines might be associated with poorer survival, although no data to date suport this hypothesis.[16-21] Although the effect of opioids and benzodiazepines has been studied, the interaction between these drug classes on clinically important outcomes (such as cognitive symptoms, gastrointestinal dysfunction, performance status, quality of life [QoL] and survival) has not been assessed.[5,6] Furthermore, toxicities have been previously explored at an individual medication-class level only.[5,6]

Aim

To explore the longitudinal relationship between oral morphine equivalent daily dose (MEDD) and oral diazepam equivalent daily dose (DEDD) with cognitive impairment, gastrointestinal symptoms, performance status, QoL and survival in patients receiving palliative care.

Methods

Study design

This study is a secondary analysis of participants in the Palliative Care Trial.[22,23] This was a prospective, 2x2x2 factorial, unblinded, cluster randomised controlled trial of academic detailing, educational outreach visits and case conferencing for palliative care patients with advanced disease and a history of pain. [5,22,23] Inclusion criteria included: expected prognosis ≥48 hours and pain in the

previous three months. Exclusion criteria included baseline Folstein Mini-Mental Status Examination score ≤24.[24] All participants were reviewed at referral, fortnightly for 3 months, and then monthly until death. Medications and doses were recorded at each visit.[6]

Sample for this secondary data analysis

Included participants had a diagnosis of cancer, symptom data recorded at baseline and at least 1 follow-up visit and a known date of death.

Variables used in this secondary data analysis

Data included in this secondary data analysis are shown in table 1.

Table 1: Data collected at baseline and follow-up

Baseline only:

1) Demographic data (date of birth, gender)
2) Diagnosis and date of diagnosis
3) Date of referral to specialist palliative care
4) Date and place of death

Baseline and at each follow-up assessment:

1) Assessment date
2) Functional assessment - Australian-modified Karnofsky Performance Status (AKPS) [25] *
3) Quality of life - McGill Quality of Life Scale (QoL) [26] **
4) Severity of symptoms – *gastrointestinal scores*: anorexia, dry mouth, constipation; and *cognitive score*: difficulty concentrating, confusion and hallucinations; and weight loss - Memorial Symptom Assessment Scale [27] ***
5) Medications - the name, dose and frequency of all medications the patient was taking ****

*Australian-modified Karnofsky Performance Status (AKPS): 0-100, lower numbers indicate a reduced performance status.
**McGill QoL scores range from 0-10, based on a mean across all domains assessed by the measure, with 0 representing the worst QoL.
***The Memorial Symptom Assessment Scale asks patients to rate the severity of each symptom from 0-4, with 4 being the worst. The three gastrointestinal symptoms were pooled for analysis (score 0-12, 12 being the worst). The same was done for the three cognitive symptoms (score 0-12, 12 being the worst).
**** Medication use was measured by calculating the oral morphine equivalent daily dose (MEDD) and the oral diazepam equivalent daily dose (DEDD).
NB: weight loss was not considered a gastrointestinal symptom as it is multifactorial

Oral morphine equivalent daily dose (MEDD) and oral diazepam equivalent daily dose (DEDD).

Calculation of oral equivalence daily dose

The Palliative Care Formulary equi-potency conversions to MEDD and DEDD were used for this analysis (Table 2).[28] There is a range of MEDDs given for each fentanyl patch dose.[28,29] A potency ratio of 150:1 for fentanyl:morphine was used.[28] As the bioavailability of the benzodiazepines used in the study was ≥80% (except midazolam), oral and parenteral were considered equipotent.[28] All benzodiazepine doses from the primary dataset were converted to DEDD at each timepoint for comparison.

Table 2: Opioid and benzodiazepine conversions used in this analysis for oral morphine equivalent daily doses (MEDD) and oral diazepam equivalent daily doses (DEDD)

Opioid and route	**Dose**	**Oral morphine equivalent**
Oral codeine	100 mg	10 mg
Oral tramadol	100 mg	10 mg
Oral oxycodone	5 mg	10 mg
Subcutaneous morphine	5 mg	10 mg
Oral methadone	1 mg	10 mg
Epidural morphine	0.1 mg	10 mg
Subcutaneous fentanyl	0.07 mg	10 mg
Benzodiazepine	**Dose**	**Oral diazepam equivalent**
Alprazolam	2 mg	10 mg
Clonazepam	0.5 mg	10 mg
Lorazepam	1 mg	10 mg
Midazolam (s/c)	5 mg	10 mg
Nitrazepam	10 mg	10 mg
Oxazepam	30 mg	10 mg
Temazepam	20 mg	10 mg
Zolpidem	20 mg	10 mg

Midazolam was only administered s/c. The other benzodiazepines have approximate dose equivalence oral or s/c, thus the same conversion was used for both routes.

All medications

For all medications, unclear, 'as-required', and undocumented doses were excluded. The route of administration was assumed to be oral unless stated otherwise. Where there was a range, the lower dose was used.

Data analysis

Each clinical outcome variable was modelled separately with multilevel modelling techniques. A basic pattern of change over time was modelled; statistically significant fixed slope estimates were taken as evidence of a change over time. Individual multilevel models were then undertaken for each covariate to explore the association. For the primary analysis, to explore the effect of MEDD and DEDD on the clinical outcome variables, individual multilevel models were undertaken. The models were further controlled for covariates with a univariate association ($p<0.10$), along with age and gender. The statistical significance was tested with a t-test (estimate/standard error) and a p-value of <0.05 was taken as significant. Key characteristics were compared using t-tests or chi-square tests. All analyses were undertaken on STATA SE (StataCorp.2015. Stata Statistical Software:Release-14. College Station,TX:StataCorp LP).

Results

Of the 461 trial participants,[22,23] those with incomplete baseline measures (n=59), <1 set of follow-up measures (n=77), a non-cancer diagnosis (n=26) or no recorded date of death (n=64) were excluded, leaving a final sample of 235 (Table 3), with 1433 study assessments.

Table 3: Characteristics of the participants

	Mean (sd), Median (Min, Max) or n (%)
Age	70.2 (12.0)
Gender	
Male	117 (50%)
Female	118 (50%)
Baseline	
AKPS	63.3 (13.1), 60 (20, 90)
Quality of Life	6.1 (1.9), 6 (0, 10)
Number of drugs	7.2 (3.5), 7 (1, 22)
MEDD dose	45.2 (114.5), 0 (0, 1280)
DEDD dose	1.1 (2.7), 0 (0, 15)
Last study visit	
AKPS	51.0 (15.7), 50 (10, 90)
Quality of Life	4.9 (2.3), 5 (0, 10)
Number of drugs	9.6 (3.9), 9 (2, 23)
MEDD dose	121.4 (202.1), 40 (0, 1200)
DEDD dose	2.6 (6.3), 0 (0, 45)
Place of Death	
Hospice	86 (36.6)
Hospital	69 (29.4)
Patient's own home	34 (14.5)
Aged care facility	17 (7.2)
Relative/close friend's home	1 (0.4)
Missing/ Unknown	28 (11.9)

Australian-modified Karnofsky Performance Status (AKPS), Oral morphine equivalent daily dose (MEDD), oral diazepam equivalent daily dose (DEDD).

Oral morphine equivalent daily dose (MEDD) and oral diazepam equivalent daily dose (DEDD).

At baseline, 96 participants (41%) were taking opioids, 43 (18%) were taking benzodiazepines and 19 (8%) were taking both. At the final assessment, 153 (65%) were taking opioids, 70 (30%) were taking benzodiazepines and 49 (21%) were taking both.

MEDD increased over the study (45.2 (114.5)mg to 121.4 (202.1)mg; p<0.001). DEDD increased from baseline (1.1 (2.7)mg to final 2.6 (6.3)mg; p<0.001).

Clinical outcome measures

Univariable analyses are shown in Table 4.

Cognitive symptom scores

At baseline the mean cognitive score (0=no symptoms; 12=maximum score) was 0.6 (SD 1.2) and increased to 1.2 (SD 1.7; p<0.001). Increased MEDD and DEDD were not related to worsening cognition after adjustment (Table 5).

Gastrointestinal symptom scores

The mean gastrointestinal symptom score (0=no symptoms; 12=maximum possible score) increased over the study period (3.0 [SD 2.4] baseline; 3.2 [SD 2.2] last assessment (p<0.001)). After adjustment, DEDD was associated with gastrointestinal dysfunction but not MEDD (Table 5).

Australian-modified Karnofsky Performance Status

Mean baseline AKPS score (range 0-100; 0 being “dead”) of 63.3 (13.1) deteriorated to 51.0 (15.7) ($p<0.001$); a change from “self-caring with occasional assistance” to “considerable assistance and frequent medical care”.[25] In the final model, worsening impairment of functional performance was associated with increasing MEDD and DEDD (Table 5).

Quality of Life

Mean McGill QoL scores (range 0-10; 0 being the worst) deteriorated from baseline (6.1 [1.9]) to last assessment (4.9 [2.3]; $p<0.001$). After adjustment, MEDD remained statistically significantly associated with worsening QoL, but not DEDD (Table 5).

Time to death

The mean survival from referral was 167.3 (SE 8.3) days. Once adjusted, higher MEDD and DEDD were not associated with shorter time to death (Table 5).

Table 4: Univariate estimates for covariates

	Cognitive symptom score		Gastrointestinal symptom score		AKPS		QoL		Time to death	
Covariate	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**
Age	0.002 (0.003)	0.319	0.009 (0.008)	0.319	-0.181 (0.031)	<0.001	0.002 (0.005)	0.591	-0.029 (0.468)	0.951
Gender (Female)	-0.212 (0.057)	<0.001	0.148 (0.208)	0.478	-33.388 (0.735)	<0.001	0.567 (0.104)	<0.001	16.308 (11.08)	0.142
Number of drugs	0.014 (0.007)	0.054	0.051 (0.018)	0.005	-0.857 (0.090)	<0.001	-0.073 (0.013)	<0.001	-12.486 (0.918)	<0.001
AKPS	-0.026 (0.002)	<0.001	-0.043 (0.004)	<0.001			0.059 (0.004)	<0.001	2.923 (0.204)	<0.001
Quality of Life	-0.154 (0.013)	<0.001	-0.281 (0.027)	<0.001	2.523 (0.158)	<0.001			13.639 (1.456)	<0.001
Weight loss	0.176 (0.029)	<0.001	0.717 (0.056)	<0.001	-1.618 (0.347)	<0.001	-0.521 (0.053)	<0.001	0.643 (3.042)	0.833
Time from assessment visit to death	-0.002 (0.001)	<0.001	-0.002 (0.001)	<0.001	0.034 (0.003)	<0.001	0.003 (0.001)	<0.001		
Time from referral to assessment date	-0.001 (0.001)	0.185	0.001 (0.001)	0.151	-0.001 (0.001)	0.367	-0.002 (0.001)	0.468		

The estimates are interpreted as the mean unadjusted absolute increase in score per unit increase in the covariate. Australian-modified Karnofsky Performance Status (AKPS), quality of life (QoL).

Table 5: Multilevel models for Oral morphine equivalent daily dose (MEDD) and oral diazepam equivalent daily dose (DEDD)

	Cognitive symptom score*		Gastrointestinal symptom score*		AKPS**		QoL***		Time to death****	
	Estimate (SE)	**p-value**	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**
MEDD										
Unadjusted	0.001 (0.001)	**0.029**	0.001 (0.001)	**<0.001**	-0.015 (0.002)	**<0.001**	-0.002 (0.001)	**<0.001**	-0.079 (0.022)	**0.001**
Adjusted	0.001 (0.001)	0.721	0.001 (0.001)	0.753	-0.009 (0.002)	**<0.001**	-0.001 (0.001)	**0.022**	-0.022 (0.023)	0.334
Adjusted plus DEDD	0.001 (0.001)	0.730	-0.001 (0.001)	0.791	-0.009 (0.002)	**<0.001**	-0.001 (0.001)	**0.022**	-0.022 (0.023)	0.332
DEDD										
Unadjusted	0.015 (0.006)	**0.009**	-0.008 (0.011)	0.461	-0.501 (0.076)	**<0.001**	-0.037 (0.012)	**0.002**	-1.381 (0.701)	**0.050**
Adjusted	0.002 (0.005)	0.777	-0.042 (0.011)	**<0.001**	-0.347 (0.071)	**<0.001**	-0.002 (0.011)	0.871	0.295 (0.689)	0.669
Adjusted plus MEDD	0.001 (0.005)	0.786	-0.042 (0.011)	**<0.001**	-0.354 (0.070)	**<0.001**	-0.002 (0.011)	0.823	0.314 (0.686)	0.648

The estimates are interpreted as the mean unadjusted absolute increase in score per unit increase in the covariate. *Adjusted for age, gender, number of drugs, Australian-modified Karnofsky Performance Status (AKPS), quality of life (QoL), weight loss and time from assessment to death. ** Adjusted for age, gender, number of drugs, QoL, weight loss and time from assessment to death. ***Adjusted for age, gender, number of drugs, AKPS, weight loss and time from assessment to death. **** Adjusted for age, gender, number of drugs, AKPS and QoL. To assess for the interaction of drugs, MEDD and DEDD were each also adjusted for each other. Adjusted values which reached significance ($p<0.05$) are in bold.

Discussion

In this study of palliative care patients enrolled in a service delivery trial, cognitive impairment, gastrointestinal symptoms, functional status, and QoL worsened towards death. Cognitive and gastrointestinal symptom scores were low throughout. Higher MEDDs and DEDDs were associated with deterioration of AKPS, higher MEDD was associated with reduction in McGill QoL scores and higher DEDD was associated with worse gastrointestinal symptoms. There was no association with survival.

In a study of palliative care patients in the last 2 days of life the median MEDD of 40mg/d, was similar to those in this study.[30] However, a group of unselected terminally ill cancer patients, the DEDD was higher (median 10-25mg/d), although this was the day before death.[30,31]

The near normal cognitive symptom scores could be a feature of the trial eligibility (Folstein Mini-Mental Status Examination score >24) and may represent a selected group at lower risk of cognitive deterioration. An apparent relationship between cognitive impairment and increased MEDD and DEDD, disappeared following adjustment; we understand little about the interplay between prescribed medications and the natural history of the disease itself.

A study of unselected opioid-treated people with cancer reported 15% with definite, and 18% possible cognitive dysfunction, associated with >400mg/d MEDD; much higher doses than in our study.[32] Perhaps MEDD or DEDD and cognitive symptoms were unrelated because the patient population was selected for better cognitive function, and/or the optimal dose monitoring in a trial context. Perhaps cognitive symptoms were under-estimated, although the item "difficulty concentrating" should detect even mild impairment. Opioids have been variably associated with cognitive impairment, hallucinations and delirium in cancer inpatients,[11-13] or not,[33,34] depending on the population, opioid or assessment tool used.

DEDD and cognitive symptoms were not associated despite previously noted associations with delirium.[12,13] This may be due to a lower susceptibility or the low DEDD (<3mg). Elderly patients admitted to hospital with normal cognition have a lower risk of developing cognitive impairment.[15] In elderly patients, benzodiazepines were not associated with cognitive dysfunction in some studies,[35,36] but were in another with larger doses; ≥5mg DEDD.[15]

The worsening of gastrointestinal symptom scores was unlikely to be clinically relevant and maybe low in the trial context. DEDD was associated with gastrointestinal scores but not MEDD despite these being well-recognised side-effects.[11,14,37-40] Benzodiazepines were associated with constipation in elderly nursing home residents.[41]

Lower AKPS was associated with an increasing MEDD and DEDD. Associations between opioid side-effects,[42] and decreasing quality of life have been reported in non-cancer conditions,[7,43,44] and benzodiazepine exposure was associated with decreasing functional status in older people.[45] No study adjusted for the effect of other drugs nor had a control arm.

Once adjusted, MEDD or DEDD and time to death were unrelated. Previously reported associations were not adjusted for stage of disease or severity of pain.[19,46] However duration and dose may be important to consider further.[21,47] We saw no dose relationship, but average survival was under six months.

Limitations

This was an exploratory analysis. The trial eligibility criteria are likely to affect generalisability, particularly regarding cognitive impairment, gastrointestinal symptoms and opioid dose. Complete removal of the effect of pre-existing deteriorating performance was not possible.

Future work

A better understanding of drug-drug interactions is needed in whole patient populations. Routine testing of cognitive function and the rapid emergence of affordable pharmacogenetics may identify sub-groups at greater risk of opioid or benzodiazepine related delirium and help target prevention.

Conclusion

Opioids and benzodiazepines were associated with deteriorating performance status and quality of life but not survival. DEDDs were associated with gastro-intestinal symptoms. Low levels of cognitive impairment may reflect the trial exclusion criteria.

Adjustment for other variables including other medications, stage of disease and severity of symptoms is important. A better understanding of the risk-benefit balance of medications, including drug-drug interactions, is needed to maximise net benefit for patients.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest

Ethics approval and consent to participate

The Palliative Care Trial was approved by all relevant independent Human Research Ethics Committees. The trial was registered with the ISRCTN on 23rd July 2003 before the first participant was enrolled, trial registration number 81117481

[http://www.controlled-trials.com/isrctn/trials/81117481/0/81117481.html]. No further ethical approval was necessary for this secondary analysis of anonymised data [http://www.hra.nhs.uk].

As this was a secondary data analysis, it was not registered as a clinical trial.

Availability of data and material

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

JB drafted the initial manuscript. VA led on the statistical analysis. All authors contributed to the study design and were responsible for the writing and approval of the final report.

Online supplement

Sensitivity analysis for those with a date of death compared with those who did not

A sensitivity analysis was undertaken on the participants who had no date of death compared to those who had a date of death. The mean time from referral to last study assessment was shorter (141.4 [117.0] days) for those who had a date of death compared to those who did not (243.5 [176.5] days). On average, those without a date of death were in the study 102 days longer and had more study visits (5.1 [3.9], median 4 [2-12], max 25 *vs* 7.2 [5.4], median 6 [2-17], max 24; p<0.001). The age was similar (70.2 [12.0] *vs* 71.8 [11.5]; p=0.350). More men had a date of death (50% vs 44%) but this did not reach statistical significance. Those with a date of death had lower AKPS at their last assessment (51.0 [15.7] *vs* 61.7 [11.9]; p<0.01). The differences between the groups were consistent with participant survival to the end of the study rather than missing data regarding dates of death. Based on this, the inclusion criterion that participants without a date of death were excluded was retained.

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